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**Case Report**

# IgA nephropathy presenting with an atypical nephrotic phenotype in an adolescent: a diagnostic challenge

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## ABSTRACT

IgA nephropathy (IgAN) is the most common primary glomerulopathy worldwide and classically presents with recurrent hematuria, variable proteinuria, and slowly progressive renal impairment. However, atypical presentations mimicking nephrotic syndrome with generalized edema and extrarenal fluid overload are uncommon, particularly in adolescents, posing significant diagnostic challenges. We report the case of a 17-year-old male admitted with progressive facial edema evolving to generalized edema, abdominal distension, dyspnea, and bilateral pleural effusion. Laboratory evaluation revealed subnephrotic-range proteinuria associated with severe nephrotic-like manifestations, including hypoalbuminemia, hypercholesterolemia, microscopic hematuria and hypertension., and transient deterioration of renal function. Initial differential diagnoses included primary nephrotic syndrome, minimal change disease, seronegative autoimmune nephropathy, and secondary glomerular disorders. Autoimmune studies, including antinuclear antibodies (ANA), anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies (ANCA), and anti-glomerular basement membrane antibodies, were negative. Renal biopsy demonstrated mesangial abnormalities consistent with IgA nephropathy, supporting the final diagnosis. The patient received multidisciplinary management with favorable clinical and renal evolution. IgA nephropathy may rarely present with an atypical nephrotic phenotype characterized by severe edema, pleural effusion, and systemic volume overload, particularly in younger patients. Histopathological assessment remains essential for diagnosis in atypical clinical scenarios. This case highlights the importance of considering IgA nephropathy in the differential diagnosis of nephrotic syndrome and underscores the relevance of integrating clinical, laboratory, and histopathological findings. In addition, a focused review of the literature is provided to contextualize uncommon nephrotic presentations of IgAN and their diagnostic implications.

**Keywords:** IgA nephropathy, Nephrotic syndrome, Adolescent, Glomerulopathy, Pleural effusion, Renal biopsy

## INTRODUCTION

Immunoglobulin a nephropathy (IgAN), first described by Berger and Hinglais in 1968, is currently recognized as the most common primary glomerulonephritis worldwide and an important contributor to chronic kidney disease and kidney failure, particularly among adolescents and young adults. Although prevalence varies geographically, the disease is especially frequent in East Asian populations, followed by Europe and Latin America, while lower incidence rates have been reported in African populations. Approximately 20-40% of patients progress to end-stage kidney disease within 20 years of diagnosis, emphasizing the clinical importance of early recognition and appropriate therapeutic intervention.[1,2]

The pathogenesis of IgAN is complex and multifactorial hypothesis. This model proposes an increased production of galactose-deficient IgA1 molecules, followed by the formation of autoantibodies directed against these abnormal glycoforms, resulting in circulating immune complex deposition predominantly in the glomerular mesangium. Subsequent complement activation,

mesangial proliferation, podocyte dysfunction, and inflammatory signaling pathways contribute to progressive glomerular injury and fibrosis. These mechanisms explain the marked variability in clinical expression and renal outcomes observed among affected individuals.[2,3]

Clinically, IgAN demonstrates a highly heterogeneous presentation, ranging from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis. The most frequent phenotype consists of recurrent episodes of macroscopic hematuria, often following upper respiratory tract infections, accompanied by microscopic hematuria, mild-to-moderate proteinuria, and hypertension. However, atypical presentations characterized by nephrotic-like manifestations despite subnephrotic proteinuria presentations have increasingly been recognized, including nephrotic syndrome, acute kidney injury, crescentic disease, and severe systemic edema, particularly in younger populations. Such atypical manifestations may delay diagnosis due to overlap with other glomerular disorders, including minimal change disease, focal segmental glomerulosclerosis, lupus nephritis, membranoproliferative glomerulonephritis, and secondary immune-mediated nephropathies.[1,4]

Histopathological confirmation through kidney biopsy remains the gold standard for diagnosis, with mesangial IgA deposition identified by immunofluorescence representing the defining pathological hallmark of the disease. In recent years, the oxford classification (MEST-C score) has significantly improved prognostic stratification by integrating histological markers associated with renal progression, including mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, tubular atrophy/interstitial fibrosis, and crescents.[3]

Despite being a relatively frequent glomerulopathy, subnephrotic-range proteinuria accompanied by generalized edema, pleural effusion, and clinically significant fluid overload remains an uncommon manifestation of IgAN, especially in adolescents. This phenotype may initially suggest alternative diagnoses and represent a substantial diagnostic challenge. Recognition of these unusual clinical patterns is particularly important because delayed diagnosis may adversely affect renal prognosis and therapeutic decision-making.[4,5]

## CASE REPORT

A young of 17-year-old previously healthy male with no significant medical or surgical history presented to the emergency department with progressive generalized edema, abdominal distension, and shortness of breath. The patient reported symptom onset approximately one month before admission, initially characterized by facial edema upon awakening that partially subsided throughout the day. Over the following weeks, edema gradually progressed to involve the abdomen and lower extremities, ultimately evolving into generalized edema (anasarca), associated with dyspnea on minimal exertion and progressive abdominal enlargement. According to the patient and his relatives, symptom onset temporally coincided with the ingestion of a natural antiparasitic preparation; however, a definitive causal relationship could not be established. The patient denied fever, rash, arthralgia, gross hematuria, or recent upper respiratory tract infection. Before hospital admission, he had received empirical treatment with oral furosemide and simvastatin without significant clinical improvement.

Physical examination revealed generalized edema characterized by facial swelling, abdominal distension with pitting edema of the abdominal wall, and severe bilateral lower-extremity edema (+++/+++). Blood pressure was 147/97 mmHg, while the remaining vital signs were within normal limits. No cutaneous lesions or joint abnormalities were identified.

Initial laboratory evaluation demonstrated persistent subnephrotic-range proteinuria, associated with marked hypoalbuminemia, generalized edema, hyper-cholesterolemia, microscopic hematuria and transient renal dysfunction, producing a nephrotic-like clinical phenotype despite the absence of nephrotic-range proteinuria. Serum albumin progressively decreased to 1.76 g/dl, accompanied by hypercholesterolemia (397 mg/dl) and hypertriglyceridemia (274.2 mg/dl). Renal function showed transient deterioration, with serum creatinine increasing to 1.54 mg/dL during hospitalization. Urinalysis demonstrated proteinuria, microscopic hematuria, and significantly increased urinary albumin excretion, with microalbuminuria of 3350 mg and an albumin-to-creatinine ratio of 2410. Complement levels remained within normal limits. Microbiological studies, including blood and urine cultures, were negative.

Imaging studies demonstrated bilateral pleural effusion and systemic volume overload. Chest radiography revealed bilateral pleural effusions, while abdominal ultrasonography identified ascites. Renal ultrasonography demonstrated bilateral nephropathy characterized by increased renal echogenicity and loss of corticomedullary differentiation, without pelvicalyceal dilatation or focal lesions. Renal doppler ultrasonography excluded hemodynamically significant renal artery stenosis.

Given the atypical nephrotic-like clinical presentation and transient deterioration in renal function, an extensive immunological workup was performed. Antinuclear antibodies (ANA), anti-double-stranded DNA antibodies, ANCA, anti-Ro/SSA, anti-La/SSB, and anti-glomerular basement membrane antibodies were all negative, reducing the likelihood of autoimmune nephritis or systemic vasculitis.

Due to the persistent nephrotic-like presentation and diagnostic uncertainty a percutaneous kidney biopsy was performed. Histopathological examination revealed

cortical and corticomedullary renal tissue containing 35 glomeruli without global or segmental sclerosis. Mild mesangial matrix expansion with preserved cellularity was observed, accompanied by neutrophils within selected capillary lumens and absence of crescents. Tubular structures demonstrated reparative changes, pigmented casts, and focal oxalate crystal deposition, without significant interstitial fibrosis. Immunofluorescence findings were compatible with IgA nephropathy, establishing the final diagnosis.

The patient received multidisciplinary management consisting of corticosteroid therapy, diuretics, antihypertensive treatment, albumin replacement, and nephrology follow-up. During outpatient follow-up, progressive clinical improvement was observed, including reduction of generalized edema, recovery of renal function, and improvement in proteinuria.

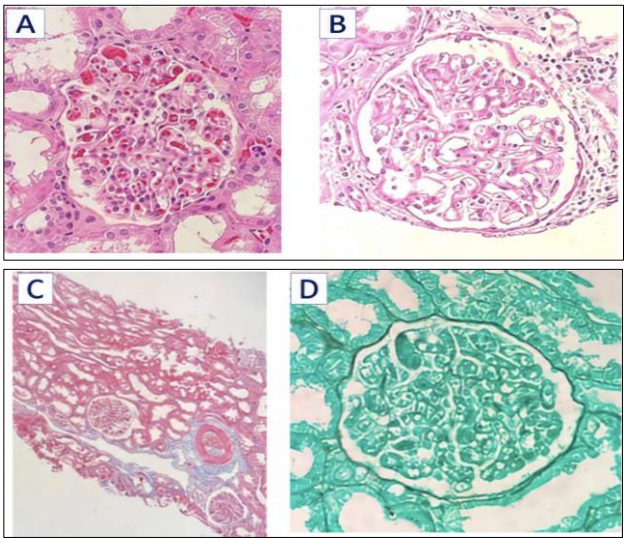


**Figure 1: Histopathological findings of renal biopsy compatible with IgA nephropathy; (A and B) glomeruli showing mesangial expansion and segmental mesangial proliferation with increased mesangial cellularity, without evidence of advanced glomerulosclerosis, observed on hematoxylin and eosin (H&E) staining; (C) renal parenchymal section demonstrating preserved corticomedullary architecture with mild tubulointerstitial involvement; and (D) special stain (trichrome/PAS) highlighting mesangial matrix expansion and relative preservation of the glomerular basement membranes. Histological findings are suggestive of IgAN.**

## DISCUSSION

IgAN is classically characterized by recurrent macroscopic hematuria, persistent microscopic hematuria, and mild-to-moderate proteinuria, often occurring after upper respiratory tract infections. In contrast, the patient described in this report presented with severe generalized edema, pleural effusion, abdominal distension, subnephrotic-range proteinuria accompanied by severe nephrotic-like manifestations and transient renal dysfunction, a phenotype considerably less common in adolescents with IgAN. Although subnephrotic-range proteinuria has been described in a minority of patients, full nephrotic syndrome with systemic volume overload remains an unusual manifestation and may obscure the underlying diagnosis. Several studies have emphasized that atypical presentations are frequently associated with delayed diagnosis and greater diagnostic uncertainty, particularly in younger patients.[6-8]

The nephrotic-like phenotype in IgAN despite persistent subnephrotic proteinuria represents a heterogeneous clinical entity that continues to be debated in the literature. Some authors propose that nephrotic manifestations in IgAN may reflect severe podocyte injury, whereas others suggest a possible overlap with minimal change disease (MCD), particularly in patients with preserved renal histology and steroid responsiveness. This subgroup, frequently termed IgA nephropathy with minimal change disease, may exhibit diffuse podocyte foot process effacement despite relatively mild mesangial abnormalities on light microscopy. Such observations are clinically relevant, as these patients often respond favorably to corticosteroid therapy and may present with a more benign long-term renal prognosis.[9]

Despite the marked edema and hypoalbuminemia, the patient never developed nephrotic-range proteinuria, making this presentation particularly unusual and diagnostically challenging. The differential diagnosis initially included primary nephrotic syndrome, minimal change disease, focal segmental glomerulosclerosis, lupus nephritis, and immune-mediated vasculitis. However, negative autoimmune serology, including ANA, anti-double-stranded DNA, ANCA, anti-Ro/SSA, anti-La/SSB, and anti-glomerular basement membrane antibodies, substantially reduced the probability of systemic autoimmune nephropathy. Similar diagnostic challenges have been reported in previous studies, where nephrotic phenotypes of IgAN initially mimicked lupus nephritis or other proliferative glomerulopathies.[10]

Histopathological findings played a central role in establishing the diagnosis. Kidney biopsy revealed mild mesangial matrix expansion with preserved cellularity, absence of crescents, and lack of global or segmental sclerosis, while immunofluorescence confirmed mesangial IgA deposition, supporting the diagnosis of IgAN. Interestingly, the relatively mild glomerular structural abnormalities contrasted with the severity of the clinical presentation, a phenomenon previously described in nephrotic phenotypes of IgAN and believed to reflect a predominant podocytopathy component rather than extensive inflammatory glomerular injury.[9,10]

The pathophysiological basis underlying nephrotic presentations of IgA nephropathy remains incompletely understood and likely differs from the mechanisms

observed in classic IgAN. Increasing evidence suggests that severe proteinuria and nephrotic syndrome may result from concomitant podocyte injury superimposed on mesangial immune complex deposition. Experimental and clinicopathological studies have demonstrated that galactose-deficient IgA1 immune complexes can activate inflammatory mediators and complement pathways, leading not only to mesangial injury but also to secondary podocyte dysfunction and disruption of the glomerular filtration barrier. This mechanism may explain why some patients, despite relatively limited structural abnormalities on light microscopy, develop profound hypoalbuminemia, generalized edema, and subnephrotic-range proteinuria, as observed in our patient.[11,12]

An additional interesting finding in the present case was the discrepancy between the severity of clinical manifestations and the relatively mild histopathological abnormalities observed on kidney biopsy. The absence of crescents, segmental sclerosis, or extensive interstitial fibrosis suggested limited chronic structural damage despite marked systemic manifestations. Previous reports have described similar clinicopathological dissociation in nephrotic phenotypes of IgAN, reinforcing the hypothesis that podocytopathy may play a substantial pathogenic role independent of severe inflammatory glomerular injury. This distinction is clinically relevant because patients with preserved histological architecture frequently exhibit better therapeutic response and renal outcomes compared with those demonstrating advanced proliferative lesions or chronic fibrosis.[9,13]

Current kidney disease: improving global outcomes (KDIGO) guidelines recommend individualized management strategies for IgAN, emphasizing supportive care, blood pressure optimization, renin-angiotensin-aldosterone system blockade, and corticosteroid therapy in selected patients with persistent proteinuria and high-risk clinical features. In nephrotic phenotypes, corticosteroids may provide substantial benefit, particularly in cases demonstrating overlapping podocytopathy or minimal-change-like features. In the present case, multidisciplinary management with corticosteroids, diuretics, antihypertensive therapy, and albumin replacement was associated with progressive clinical improvement, reduction of edema, recovery of renal function, and improvement in proteinuria, findings consistent with previous reports describing favorable responses in atypical nephrotic presentations of IgAN.[1,14]

From a prognostic perspective, this case suggests that the severity of clinical manifestations does not always correlate with the degree of proteinuria or the extent of histopathological injury in IgA nephropathy. Despite severe edema, marked volume overload, and transient impairment of kidney function, the kidney biopsy revealed only mild mesangial lesions, without significant glomerulosclerosis or crescent formation, findings that likely contributed to the favorable clinical outcome following treatment. This clinicopathological dissociation underscores the importance of integrating histopathological findings with the overall clinical assessment to establish prognosis and guide therapeutic decision-making, rather than assuming an aggressive disease course based solely on the initial presentation.

## CONCLUSION

IgAN may present with atypical clinical phenotypes an atypical nephrotic-like phenotype characterized by generalized edema, pleural effusion and persistent subnephrotic-range proteinuria.

This case emphasizes the importance of maintaining a broad differential diagnosis in young patients presenting with nephrotic syndrome and systemic fluid overload, especially when autoimmune and infectious studies are negative. Kidney biopsy with immunofluorescence remains essential for establishing the definitive diagnosis and differentiating IgA nephropathy from other immune-mediated nephropathies.

Early recognition and timely multidisciplinary management may contribute to favorable renal outcomes, particularly in patients with limited chronic histopathological damage and good therapeutic response. Furthermore, this report highlights the need for increased awareness regarding uncommon nephrotic phenotypes of IgA nephropathy and their implications for diagnosis and treatment.

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